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WHAT RESEARCH WITH STORED SAMPLES TEACHES US ABOUT RESEARCH WITH HUMAN SUBJECTS

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ABSTRACT

There is widespread discussion concerning the safeguards appropriate for human research subjects. Less discussed is the fact that the safeguards one deems appropriate depend, in large part, on the model of research participation that one assumes. Therefore, to determine what safeguards are appropriate, it is necessary first to clarify the competing models of research participation. The ostensibly obscure debate over informed consent for research on stored biological samples is of particular interest in this regard because such research can involve varying subsets of the three central elements of research involvement. As a result, analysis of this debate provides an opportunity to identify the competing models of research participation. Based on this analysis, this paper describes a new model of research participation that is emerging, and considers its implications for clinical research.

To implement human subjects protections, one must first identify which individuals are involved in research. Most analyses address this need by assuming some paradigm cases of research involvement, for instance, an individual with metastatic cancer receiving experimental treatment as part of a research protocol. Although this reliance on paradigm cases is sufficient in many cases, it obscures the fact that involvement in research includes three distinct elements: 1. *exposure* to risks; 2. *performance* of research mandated behaviors; 3. *contribution* to answering a research question. Without further analysis, then, it is unclear whether the need for human subjects protections is a function of all three elements, or some subset of them.

To consider a specific example, the standard drug trial involves individuals facing risks (risk element) as a result of taking an

experimental drug (performance element) in a way that helps investigators determine whether the drug might be clinically useful (contribution element). Because all three elements co-occur in the standard cases, it is unclear which one(s) ground the need for familiar human subjects protections: Do investigators need to obtain the informed consent of individuals who participate in drug trials because they are being exposed to risks and/or because they are being asked to take certain medicines and/or because they are contributing to a specific research project?

Research on stored biological samples offers a surprising opportunity to answer this question because it can involve varying subsets of the three elements of research involvement. For instance, research on personally identified stored samples can pose risks to sources even though investigators never interact with the sources or ask them to do anything. The present paper attempts to identify the competing models of research involvement by assessing when research with stored samples is thought to require human subjects protections.

The present discussion, particularly as it concerns human subject regulations, focuses on the situation in the United States. In part, this is because much of the discussion concerning research on stored samples has been occurring in the United States. Moreover, limiting the discussion to the situation in a single country allows me to bracket any cross-national differences in policies regarding research with stored samples and focus on the relevant conceptual issues.

THE CURRENT DEBATE

When should investigators obtain sources' informed consent for research on stored biological samples? Most writers agree that investigators need not obtain sources' informed consent for research on completely anonymous samples. And many agree that investigators should obtain informed consent for research on samples that retain personal identifiers. This consensus has focused much of the debate on research using 'anonymizable' samples – samples that have personal identifiers which, for the purposes of the research, could be removed before the research is conducted.

The U.S. College of Medical Genetics argues that whether research on anonymizable samples requires sources' consent depends upon how burdensome it would be to obtain it.[1] Most

[1] American College of Medical Genetics. Statement on storage and use of genetic materials. *Am J. Hum. Genet.* 1995; 57: 1499–1500.

accounts evaluate different levels of burden based on the research's risks. When research poses only minor risks, there is little reason to solicit sources' consent; hence, almost any level of burden required to contact them would be deemed excessive. However, as research poses increasing risks to sources, investigators should be required to accept increasing burdens to obtain their consent.

The primary risks of research on stored samples involve unwanted information flow. Such research may reveal facts about sources, and their futures, that they did not know, and did not want known.[2] Anonymizing samples eliminates these risks by eliminating the possibility of tracing results back to sources. Thus, on the view that the burden of contacting sources should be evaluated against the risks of the research, investigators need not solicit sources' consent for research on anonymizable samples. Instead, investigators can anonymize the samples and proceed with their research (provided anonymizing samples is consistent with the goals of the research). Reilly, Boshar and Holtzman: 'Truly anonymous studies circumvent the need to address ... issues such as fear of unauthorized release of genetic information ...'[3] In the supporting words of the American Society of Human Genetics (ASHG): anonymizing samples protects sources from the risks of genetic research and thus 'eliminates the need for recontact to obtain informed consent.'[4]

Critics respond that this view ignores much of the point of obtaining sources' informed consent. In addition to notifying sources of any risks, informed consent allows sources to control whether their samples are used for research purposes. On this

[2] Research on stored samples may also reveal unwanted facts about the *groups* to which sources belong. However, to simplify things, I shall focus on research that poses risks only to the individuals involved in the research. (I shall also assume that the research under consideration does not offer any potential for medical benefit to subjects.) Group risks are of theoretical interest because they present the possibility that individuals may be harmed by research they do not participate in. Adopting the terminology used below, this possibility reveals that protocols which require consent on the subject model are not, as one might initially suppose, a subset of the protocols which require consent on the experiential model. The U.S. NBAC considers this issue briefly in its report 'Research Involving Human Biological Materials: Ethical issues and Policy Guidance', *Report and Recommendations of the National Bioethics Advisory Commission*. Vol. I. Rockville, MD. August 1999: 73.

[3] P.R. Reilly, M.F. Boshar, S.H. Holtzman. Ethical Issues in Genetic Research: disclosure and informed consent. *Nat. Genet.* 1997; 15: 17.

[4] The American Society of Human Genetics. Statement on informed consent for genetic research. *Am. J. Hum. Genet.* 1996; 59: 473.

basis, an Ethical, Legal, and Social Implications of the human genome project (ELSI) working group argues that sources' consent should be obtained whenever possible: 'if the source can be identified, that source should be asked for his or her consent.'[5] Similarly, participants in a workshop on research with tissue samples concluded that anonymizing samples based on the absence of any risks to subjects is: 'problematic because researchers had an opportunity to seek consent but did not exercise it.'[6]

Importantly, these two approaches adopt the same view when samples lack personal identifiers and when removal of personal identifiers would be inconsistent with the scientific goals of the research. In the first case, those who understand informed consent as a mechanism for notifying sources of potential risks argue that the research can proceed without consent because anonymizing the samples eliminates any risks. Those who understand informed consent as a mechanism for allowing sources to control whether their samples are used for research purposes agree, in this case, because the anonymity of the samples eliminates the possibility of contact. When personal identifiers cannot be removed, the emphasis on risks implies that informed consent should be obtained in order to notify sources of the risks. Those who emphasize allowing sources to control the use of their samples agree because the personal identifiers provide investigators with the opportunity for contact.

Research on samples with personal identifiers that can be removed is of theoretical interest because it is here that the two dominant views on obtaining sources' consent diverge. Those who focus on risks recommend that investigators anonymize samples and conduct their research without sources' consent; those who emphasize allowing sources to control the use of their samples argue that the identifiers should be used to contact sources. The claim that informed consent may be waived for anonymizable research appears to trace to the earliest model for understanding clinical research. Early on research procedures tended to pose risks to subjects without much chance of medical benefit. Add to this the fact that the most egregious research abuses involved individuals being subjected to especially risky

[5] NIH-DOE Working Group on the Ethical, Legal, and Social Implications of Human Genome Research. February, 1995. ELSI Working Group Statement on Research on Previously Collected Tissue Samples: 1.

[6] E.W. Clayton, K.K. Steinberg, M.J. Khoury, et al. Informed consent for genetic research on stored tissue samples. *JAMA*. 1995; 274: 1788. I note that not everyone in the workshop agreed with this view.

procedures, and one gets the view that individuals' involvement in clinical research is defined by the risks they face, by what they are being subjected to.[7]

A number of writers have pointed out that research can affect individuals, by having them do things or doing things to them, even when it poses no risks to them. Given that individuals have an interest in what happens to them, these writers conclude that investigators should obtain individuals' informed consent whenever research affects them personally. To take a notable example, Robert Veatch argues that the doctrine of informed consent is based, not on individuals' right to avoid risks, but on their right to control the course of their lives.[8] The U.S. National Commission agreed, defining a human subject as a 'person about whom an investigator conducting scientific research obtains data through intervention or interaction with the person.'[9] Current U.S. federal regulations on human subjects research are based on this 'experiential' model, rather than the earlier subject model.[10]

Although the experiential model offers the most prominent alternative to the subject model, it does not imply that investigators necessarily ought to obtain sources' informed consent for anonymizable research. For instance, when samples have been obtained, and will be anonymized, sources are unaffected by whether the research takes place or not. Hence, those who base the need for informed consent on individuals' right to control the course of their lives have no reason to require sources' consent in these cases. The fact that some writers argue for sources' consent, nonetheless, suggests that they are appealing to some third model of research involvement.

The alternative models of research involvement can be characterized in terms of alternative accounts of individuals'

[7] For instance, the earliest U.S. regulations for ethics review committees (IRBs) define a subject of research as an individual who 'may be at risk.' DHEW. 1971. The Institutional Guide to DHEW Policy on Protection of Human Subjects. Publication No. (NIH). Washington, D.C. U.S. Govt Printing Office: 72–102.

[8] R. Veatch. 1978. Theories of Informed Consent: Philosophical Foundations and Policy Implications. The Belmont Report. Appendix II DHEW Publication No. (Os) 78–0014. Washington, D.C. U.S. Govt Printing Office.

[9] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1978. Report and Recommendations: Institutional Review Boards. DHEW Publication No. (OS) 78: 0008. Washington, D.C. U.S. Govt Printing Office.

[10] United States Department of Health and Human Services. 1991. Protections of Human Subjects. Title 45 Code of Federal Regulations Part 46.102 f.

relevant interests. The subject model traces to the claim that individuals' primary interests relevant to research are their interests in avoiding harm. On this view, whether specific individuals are involved in research in a way that should trigger human subjects protections depends upon whether the research poses risks to them. The experiential model recognizes a broader range of interests as relevant to individuals' research involvement, requiring that one consider whether the research might affect the individuals in any way, not simply whether it might harm them. The impetus for a possible third model for understanding research involvement starts with the question of whether individuals have interests relevant to clinical research independent of the risks it poses, or how it affects them personally.

SOURCES' INTERESTS AND THE ARGUMENT FROM CONTRIBUTION

To start, what reason could there be to solicit sources' informed consent for research that poses no risks to them and does not affect them personally? What is left for sources to consent to? Stripping away how the research affects sources personally leaves the research itself: why it is being conducted, what its goals are, who is supporting it, and so on. This suggests that any plausible argument for obtaining informed consent for research on anonymizable samples will have to show that sources should be able to determine whether their samples are used for specific research purposes independently of whether these projects affect them personally. One way to defend such a position is by means of the following 'Argument from Contribution':

1. Sources have an interest in whether their samples are used for specific research purposes independently of whether the research affects them personally.
2. Individuals should have a say in states of affairs in which they have an interest.
3. Therefore, sources should have a say in whether their samples are used for specific research purposes independently of whether the research affects them personally.
4. For sources to have a say in whether their samples are used for specific research purposes, investigators must obtain their informed consent.
5. Therefore, investigators should obtain sources' informed consent even when the research does not affect them personally.

Starting with the second premise, one can think of an individual's interests as referring to the various aspects of a flourishing life for that individual: if X is part of a flourishing life for P, then P has an interest in (the obtaining of) X.[11] Conversely, if X conflicts with a flourishing life for P, then P has an interest in X's not obtaining. For the most part, the various aspects of a flourishing life are states of affairs. So, for instance, on the assumption that a flourishing life includes good health and close personal relationships, individuals have an interest in the obtaining of these states of affairs.[12]

In addition to the obtaining or not of specific states of affairs, the flourishing life also includes some degree of personal autonomy. It is not important simply that particular states of affairs come about, that one's life consists of a series of desirable states of affairs. A flourishing life also involves individuals actively shaping their own lives by determining what experiences they have and what projects they contribute to. Of course no one gets to control every aspect of one's life, and no sane person would want to. As will be important later on, individuals can cede control over certain aspects of their lives without them being any less human or any less flourishing.

It is important to distinguish two aspects of having a say over a particular state of affairs: the *weight* of one's claim to have a say and the *nature* of one's say. The weight of an individual's claim to a say is a function, roughly, of how central the state of affairs is to their life.[13] Individuals have a weighty claim to a say over those states of affairs that are central to their lives, such as the careers they follow, whether they marry, and what happens to their appendages, and a less weighty claim over states of affairs less central to their lives, such as who their neighbors are. The weight of one's claim to a say provides a rough measure of the burdens

[11] The states of affairs in which P has an interest should be contrasted with the states of affairs in which P is interested. For a (brief) account of the latter, see S. Kagan. 1989. *The Limits of Morality*. Oxford. Oxford University Press, especially p. 3.

[12] Roughly speaking, which states of affairs count as aspects of a flourishing life for P can be understood objectively or subjectively. On an objective account, it is simply a fact, independent of P's psychology, that certain things are part of a flourishing life for her. On a subjective account, whether X is part of a flourishing life for P depends in some way on P's psychology, for instance, on P's actual or idealized *preferences*.

[13] 'Weight' in the sense intended here is often understood in terms of the 'strength' of the relevant desire (for instance, see Griffin p. 15). I avoid this terminology because it invites confusion with strength understood as felt intensity or motivational force.

society must accept in respecting one's say. Since I have a very weighty claim to determine what happens to my body, only societal interests of the highest order can outweigh my say over what happens to my body.

The *nature* of the say that one has over a particular state of affairs is, roughly, a measure of the extent to which one gets to determine whether the state of affairs comes about. A plausible assumption is that the nature of one's say is determined by the weight of one's claim to having a say. If I have a very weighty claim, then I get the determinative voice, and if I have a much less weighty claim, I get, in effect, only a single vote. In fact, the nature of one's say also depends upon the extent to which others have a say. For instance, I have a weighty interest, and typically others do not have a weighty interest, in issues central to my life, such as what happens to my body. It follows that my weighty interest in what happens to my body often implies that I get to control this aspect of my life. But this is not always the case. Forced military service involves my weighty claim to having a say over what happens to my body being overridden by the competing weighty claims of others to national defense. At the opposite extreme, my very weak claim to having a say over a particular state of affairs, what happens to a particular sea shell, for example, can amount to de facto personal control because no one else has any claim over the state of affairs in question.

Granting that one often does not get personal control over the states of affairs in which one has an interest, it might seem that one nonetheless gets personal control over whether one contributes to the state of affairs in question. Others may be able to outweigh my vote for mayor, but they cannot force me to vote for a specific individual. In fact, control over one's own contribution is defeatable as well. The example of individuals being forced to serve in the military and, thereby, forced to contribute to the war effort, is one example. Similarly, individuals who strongly oppose urban sprawl do not get to decide whether their tax dollars are used to connect the newest executive suburb to the opera house.

To this point, the discussion has been concerned primarily with states of affairs that affect individuals personally – whether they marry, what happens to their bodies. In these cases, it is plausible to argue that individuals should have a say because it is plausible to say that they have an interest. It is less obvious, as premise 1 of the Argument from Contribution assumes, that individuals also have interests in states of affairs that do not affect them personally. Indeed, one might assume that without the

possibility of a personal experience, there is no ground on which to base an interest, no way in which the state of affairs in question could be about one's life.

NON-EXPERIENTIAL INTERESTS

Certain states of affairs can be part of a flourishing life for us, hence, we can have an interest in whether these states of affairs obtain, even though they never affect us personally. To take a concrete example, individuals' future driving records can have implications for their driving instructors' lives. Whether the students were taught well, and go on to spotless records, or weren't and go on to many accidents, is relevant to the instructors' lives. It says something about how well the students were taught, hence, something about how good the instructors were. Notice that this implication remains even when the students' driving futures do not affect the instructors personally, for instance, even when the students never have an accident with their instructors. The fact that we can have interests in states of affairs that do not affect us personally raises the question of what, if not one's personal experiences, determines the scope of one's interests.

Consider Derek Parfit's example of meeting a stranger on a train, finding out that he may have a fatal disease, and developing a desire that things work out for the best.[14] Presumably, it would be a good thing if, six months later, the stranger is cured. However, as Parfit points out, the stranger's cure is not in Parfit's interests, despite the fact that Parfit may be very interested in whether the stranger is cured. The reason, Parfit argues, is that one has interests in only those states of affairs that are 'about one's own life.'

Although this sounds right, it presses the question of which states of affairs are *about* one's life. Why is the future fate of driving students relevant to their instructors' lives, but the future health of the stranger isn't relevant to Parfit's life? Notice that the answer does not depend upon the *strength* of the individual's desire. Parfit may desire the stranger's cure more than the instructor desires the future safety of his ex-students. Nonetheless, the stranger's cure does not seem to be about Parfit's life in the way that the students' driving futures are about their instructor's life. How might we explain this difference?

[14] D. Parfit. 1984. *Reasons and Persons*. Oxford. Oxford University Press: 494.

James Griffin suggests that, in addition to what we experience directly, our interests also include those states of affairs that 'I take into my life as an aim or goal.'[15] On Griffin's account, although Parfit desires the stranger's return to health, he does not, as the story goes, take this on as a personal goal: he does not commit himself to working to bring about the stranger's cure.

Griffin's crucial insight is that mere desiring is not sufficient to ground an interest because it is too passive. The fact that I take on a particular goal makes the state of affairs referred to a part of my life in the sense that this is now one of my goals. However, it does not seem to follow that the occurrence of the state of affairs in question necessarily has implications *for* my life. We would not say that I lived a better or worse life simply because this goal of mine is or is not realized; it depends upon *how* the goal is realized.

We assume, in the standard cases, that once an individual takes on a particular goal, she will actively work toward realizing that goal. The problem for Griffin's account is that such activity is not required by the mere fact of having the goal – one can have goals that one does nothing to bring about (although the fact that one does nothing may provide evidence that one does not really have the goal in question). Imagine that after worrying for several weeks, Parfit takes on the stranger's cure as a personal goal. If the stranger is cured, we would not say, now that this is one of Parfit's goals, that Parfit's life is necessarily better for it. In a similar way, we do not say that the students' future driving records say something about the instructor's life simply because she has the goal, assuming she does, of her students being accident free. We say this because the instructor actually did something to realize this goal: she taught her students how to drive. Indeed, in this case at least, the instructor's contribution seems to render irrelevant her having the relevant goal, or even the relevant desire. Even if the instructor develops the strong desire that her ex-students crash and burn, their future driving records would still say something about what kind of instructor she was.[16] Put generally, *working* toward a particular goal entails that its realization says something about one's life because it is

[15] J. Griffin. 1986. *Well Being*. Oxford. Oxford University Press: 22.

[16] The instructor could make more substantial changes which might entail that the students' driving futures is no longer in her interest. For instance, she might decide to commit herself to a life of helping as few people as possible. In some such cases (particularly if one accepts a subjective account of a flourishing life), we might want to say, given this change, that the students' future driving records are no longer in, and may even be contrary to the instructor's interests.

now, in an important sense that it was not before, one's own project.[17]

The present line of reasoning suggests that we can have interests in states of affairs that do not affect us personally because we can contribute to whether they obtain.[18] And this suggests that the confirmation of the first premise in the Argument from Contribution – sources have an interest in whether their samples are used for specific research purposes independently of whether the research affects them personally – requires showing that sources contribute (in the relevant sense) to such research.

THE NATURE OF SOURCES' CONTRIBUTION

A number of pathologists have pointed out that non-genetic (e.g. epidemiological) research on stored samples has been going on for years without bioethicists, or anyone else, claiming that the researchers need to obtain sources' informed consent. Since genetic research with *anonymized* samples is no more risky, and has no more effect on individual sources, this argument suggests that investigators should be able to conduct genetic research on anonymized samples without sources' informed consent. Before considering whether this view is right, consider the following: why did the advent of widespread genetic research trigger demands that researchers obtain sources' informed consent in a way that earlier epidemiological research had not?

Part of the answer, I suspect, is that genetic research is newer and we have less sense of what it might lead to. As a result, we tend to judge it as being riskier. Granting this, epidemiological research also typically involves investigators analyzing fairly general properties of the tissue in question. For instance, epidemiologists consider whether individuals who received drug

[17] To press Griffin's account further, it seems that the stranger's cure being about my life requires that I actually make a contribution, not simply that I attempt to do so. If I send the stranger money for new treatments, but he is cured before it arrives, then his cure is not about my life. Even though I took on his cure as a personal goal and tried to do something to realize this end, I did not in fact make a contribution.

[18] A related question arises here. Do individuals have an interest in controlling information about them independent of their own experiences or the projects to which they contribute? On the present account it is not clear that they do. However, some have concerns about the availability of personal information per se and seem to regard it as relevant to their lives. In the end, this may not be a complete account of individuals' interests, but it does capture the interests that are relevant to the debate over anonymized research.

X developed abnormality Y at an increased rate relative to the general population. In contrast, genetic research often involves investigators analyzing individual properties of a given tissue sample. When searching for the genes implicated in breast cancer, investigators search extended regions of sources' genotypes to isolate the differences between those who develop the disease versus those who don't. In this case, the individual properties of the sources' DNA become central, the investigators are no longer analyzing various tissues, they are analyzing the tissue of specific persons. As a result, it seems more plausible to argue that the persons in question make an individual contribution to the research.

The sense that sources make a personal contribution to genetic research is reinforced by historical views on genes. Historically, many people have viewed the genetic code as central to, and even constitutive of, one's identity. Given this presumed strong connection between individuals and their DNA, it is not surprising that people would regard the use of tissue samples for genetic research as representing more of an individual contribution to that research than the use of tissue samples for epidemiological research.

The subject model defines individuals' involvement in clinical research in terms of their exposure to research risks, while the experiential model defines research involvement in terms of individuals interacting with investigators and being asked to do certain things. The present line of reasoning suggests a third model that understands individuals' involvement in clinical research in terms of their making a contribution to particular research projects. Although I cannot provide a complete account of the contribution model here, it will be important to understand the nature of individuals' possible contribution to research.

On the 'contribution' model, whether an individual is involved in clinical research, hence, whether human subjects protections apply to them, can be understood in terms of whether information about the individual is used to answer the scientific question being asked. Put simply, whether an individual is a contributor to a research project in this sense depends upon whether information about the individual will be included as data in the analysis of the study. If it will be, then the individual is a contributor to the research project. And since individuals have an interest in the projects to which they contribute, it follows that individuals who contribute in this way have a claim to a say over whether they make this contribution. Therefore, to the extent sources contribute to genetic research in this sense, they have an

interest in how their samples are used whether or not the research affects them personally.[19]

Research on stored samples helps to distinguish the experiential model from the contribution model by clarifying at least one way in which an individual's contribution to a research project need not be active. In particular, it clarifies that one can contribute to a research project in the sense that one's DNA is included in the project's data analysis without one having to do anything for the project, indeed without one even having to know of the project's existence. In the standard cases, all that is required is that one provided a DNA sample, along with information about one's phenotype, and the investigators now include correlations between the two in their data.

Although the stored sample debate helps to distinguish the three models of research involvement, it is important to recognize that such research is unusual in this sense. In the standard cases, individual's involvement in research involves all three elements. That is, although the three models present alternative understandings of involvement in research, they do not present mutually exclusive understandings. Recognizing the contribution model as a distinct way of conceptualizing research involvement helps to clarify an otherwise anomalous feature of the debate in the U.S. over consent for research on stored samples.

THE IMPORTANCE OF WHEN SAMPLES ARE OBTAINED

The U.S. federal regulations do not apply to research on *existing* tissue samples provided: 'the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers.'[20] As a result, investigators who

[19] One could argue that the contribution model is simply an expansion on the experiential model (as opposed to a new model of research involvement) in the sense that the contribution model recognizes an additional aspect of individuals' experience, contributing to a research project, as relevant to their research involvement. In the end, it is not clear that any substantive issues hang on whether one considers the contribution model to be a new model versus a new expansion of an old model. With that said, there is an important question of why the three models of research involvement emerged in this particular order – subject, experiential, contribution? Briefly, I suspect the answer has to do with the research community's coming to recognize an increasingly broader range of subjects' interests relevant to their research participation.

[20] United States Department of Health and Human Services. 1991. Protections of Human Subjects. Title 45 Code of Federal Regulations Part 46: 1014.

plan to anonymize previously obtained samples prior to the initiation of their research are not required to obtain ethics review committee (IRB) approval, nor sources' informed consent. The 'preamble' to the regulations explains why not: 'In developing the HHS proposed regulations care was taken to provide protection for human subjects involved in those activities that present risk to subjects, while exempting from coverage by the regulations many forms of research that do not involve risks or involve only slight or remote risks.'[21]

The U.S. regulations' treatment of samples that will be obtained in the future is very different. Research on tissue samples that will be left over, and made anonymous, following future clinically indicated surgery does not pose any risks to the sources. Nonetheless, in this case, the lack of risks is not deemed sufficient to waive ethics review and sources' consent. Instead, research on samples yet to be obtained must undergo ethics review. In addition, such research must obtain sources' informed consent unless it 'could not practicably be carried out without the waiver [of informed consent].'[22] In other words, in moving from previously obtained to prospectively obtained samples, the U.S. federal regulations move from a default of waiving consent to one of requiring consent.

The ASHG also changes its proposed safeguards as it moves from research on existing samples to research on samples that will be obtained prospectively. In the former case, the ASHG endorses waiving informed consent; in the latter case, the ASHG recommends that investigators 'communicate with potential subjects in advance and involve them in the research by obtaining informed consent.' To take one more example, the U.S. National Bioethics Advisory Commission (NBAC) endorses waiving sources' consent for minimal risk research on existing samples on the grounds that doing so does not pose any risks to sources, and does not threaten their rights and welfare. Why then doesn't the NBAC recommend waiving informed consent for research on samples that will be obtained in the future provided the research poses minimal risks and the waiver of consent does not jeopardize sources' rights and welfare?

When samples are obtained does not necessarily affect a protocol's risks or potential benefits, nor what the protocol asks of sources. Nonetheless, it may affect how one conceptualizes the

[21] Federal Register. 1981. Final regulations amending basic HHS policy for the protection of human research subjects. 46: 8369.

[22] *Op. cit.* note 20, page 116.

role of sources. When it comes to research on *existing* tissue samples, the interaction between sources and those obtaining the samples has already occurred, the sources fade from view and, in evaluating the research, one is left with the interaction between an investigator and a clump of cells. Given that this interaction does not include sources, one has less reason to consider whether they might have any interests in whether they contribute to the research in question. Instead, one assesses only whether they face any risks. In other words, one adopts the subject model of sources' role.

Changing the example to one in which the samples will be obtained tomorrow, rather than yesterday, does not necessarily change whether the research will affect sources. However, it does change the interaction that one focuses on in evaluating the research: one considers the removal of samples from people's bodies rather than laboratories' refrigerators and ends up with the contribution model. The tense is relevant to the need for informed consent, then, because it brings the sources into view, thus raising the expectation that investigators will consider their broader interests.

I should point out that although the prospect of obtaining tissue in the future leads many to adopt the contribution model, it does not affect everyone in this way. The College of American Pathologists (CAP) argues that the U.S. federal regulations' exemption for research on existing samples should be expanded to cover research on samples that will be obtained prospectively, provided the samples are obtained for clinical reasons and the tissue is left over after 'all work necessary for the patient's care has been completed.'[23] In effect, the CAP is asking that the U.S. federal regulations apply the subject model consistently. This makes sense. For the most part, pathologists deal with tissue, not sources. Even when the tissue is obtained tomorrow, pathologists will not be interacting with the sources. Thus, they are never in a position of taking tissue from sources while wondering whether the sources have any preferences on how the tissue will be used. Finally, identifying the contribution model as distinct from the subject and experiential models allows us to consider its practical implications.

[23] College of American Pathologists. Uses of Human Tissue. 1996: 7. (A consensus statement by the College of American Pathologists and 16 other organizations, available from the college at 325 Waukega Road, Northfield, IL, U.S.A 60093 or http://www.cap.org/)

PRACTICAL IMPLICATIONS

Imagine that an investigator is offered any tissue samples that are left over after clinically indicated surgery that will be performed in two months. If the investigator submits her proposal to conduct research on these samples to the ethics review committee *before* the samples are obtained, the ethics review committee would be reviewing a proposal to conduct research on prospectively obtained samples. Hence, under the U.S. regulations, the protocol would have to obtain ethics review, as well as sources' informed consent provided it can be obtained practicably.

With this in mind, a savvy investigator doing exactly the same research could avoid the requirement for informed consent simply by delaying submission of the protocol until after the samples have been obtained, at which point the ethics review committee would be reviewing a proposal to conduct research on existing samples. Assuming the now-existing samples are anonymized, the research would be exempt from ethics review, hence, the researcher would not be required to obtain sources' informed consent.

As the U.S. regulations turn to existing samples, they shift to the subject model. In the process, the requirement to obtain sources' consent when it is practicable to do so drops out. Using this loophole, unsavory investigators could obtain tissue samples under an innocuous research study and then propose a controversial study for which the investigator has reason to believe sources would not have consented. Since the research now involves existing stored samples, the investigator could avoid ethics review and the need for sources' consent by anonymizing the samples.

Next, the U.S. ELSI working group argues that: 'Any proposals for anonymous research on previously stored tissue samples should be reviewed by an IRB (ethics review committee).'[24] Along the same lines, Clayton et al. suggest that ethics review committees could 'usefully review research proposals to [ ] make currently identifiable tissue samples anonymous without the sources' consent.' The proposal continues: 'Some participants urged that consideration be given to amending the regulations to require such reviews.'[25] Even Knoppers and Laberge, who question these recommendations on several counts, agree with

[24] *Op. cit.* note 6, p. 1788.
[25] *Ibid.*

this suggestion: 'Clayton et al. wisely suggest IRB review before removal of identifiers.'[26]

Presumably, this suggestion seems wise because the risks of genetic research are largely unknown. Therefore, rather than develop a general policy on when sources' informed consent should be required, and when samples can be anonymized without consent, it makes sense to allow an independent group to make this determination on a case by case basis. Unfortunately, given the current U.S. regulations, this recommendation is not as neutral as it might appear. The requirement that all research proposing to anonymize tissue samples first undergo ethics review would result in investigators having to obtain informed consent whenever doing so is 'practicable'. On the assumption that it is practicable to obtain sources' consent in many cases, this requirement would lead to an unintended increase in the number of times that investigators would be required to obtain sources' consent. To address these practical difficulties, consider the possibility of applying the contribution model consistently to all research using biological samples.

POLICY IMPLICATIONS FOR RESEARCH ON BIOLOGICAL SAMPLES

The weight of individuals' claim to a say over whether they contribute to a particular research project depends upon how central making this contribution is to their lives. In the majority of cases, it seems plausible to assume that it is important for individuals to determine whether their samples are used for research purposes since doing so allows sources to decide whether they contribute to the general project of increasing medical knowledge and helping others. This suggests that sources have a moderately weighty claim to determine whether their samples are used for research purposes at all. It seems less important, in most cases, for individuals to control whether their samples are used to study one disease or another. Whether I contribute to medical research at all says something important about my life; whether I contribute to research on arthritis as opposed to research on diabetes says less about my life. This suggests that, in general, sources have a less weighty claim to determine precisely for which research projects their samples are used. However, the specific nature of certain research projects

[26] B.M. Knoppers, C. Laberge. Research and Stored Tissues: persons as sources, samples as persons? *JAMA* 1995; 274: 1807.

can give sources a weighty interest in determining whether their samples are used. For instance, some oppose abortion and dedicate their lives to ending its provision. Such individuals have a weighty interest in controlling whether they contribute to research projects that involve abortion.

The weight of individuals' claims to having a say must be balanced against any interest they have in *not* having a say. To obtain individuals' informed consent, investigators must first provide them with information about the study. For instance, with respect to research on stored samples, sources might be told that, if they agree, their DNA will be tested for a particular mutation. In certain instances, sources may be better off without this information. Knowing that one's DNA is being tested for a particular mutation may put individuals in the position of having to decide whether to inform their employers that their DNA may have tested positive for this mutation. Given that employers may use this information to the individual's detriment, the process of informing sources could put them in the position of having to lie or disclose potentially harmful information.

To balance sources' interests in having a say against their occasional interest in not being given certain information requires an assessment of the risks of being informed in particular cases. Might being informed of the nature of a particular study jeopardize sources' jobs or insurance status? Is there evidence that the information in question poses risks to family members? The answers to these questions will depend upon the kind of study in question and, thus, must be assessed on a case by case basis.

Sources' moderately weighty interest in determining whether their samples are used for research purposes at all suggests that their consent should be required for research using samples for which consent for research purposes has never been obtained. Once consent for research purposes has been obtained, sources' less weighty interest in determining the specific projects to which they contribute suggests that investigators should obtain consent for additional research studies provided it is relatively easy to do so. This suggests that something like the practicability standard should be applied to all research, even research that involves previously obtained samples. When contacting sources is not feasible, consent can be waived provided consent for research purposes has been obtained previously, and there is no reason to think that the research in question is central to sources' interests in the way that research on abortion is for some.

The claim that individuals can make a contribution to research on stored samples that does not affect them personally is not

limited to genetic research. To take an earlier example, sources contribute to epidemiological research in the sense that some of their tissue is used to conduct the research in question. Thus, on the contribution model, investigators have a reason to obtain sources' consent for epidemiological research even when the research will be done anonymously. However, for reasons discussed earlier, sources make less of a personal contribution to epidemiological research. As a result, they have less of an interest in controlling whether they contribute to such research and investigators have less of a reason to solicit their consent. Two conclusions are possible here.

First, one could conclude that epidemiologists ought to solicit sources' informed consent when it is relatively easy to do so. Alternatively, one might conclude that since sources' interest in epidemiological research is less weighty, the burden of obtaining consent outweighs sources' interests in having a say. In support of this approach, and pending empirical evidence to the contrary, it seems plausible to assume that epidemiological research represents an example of research for which sources are willing to allow investigators to decide whether their tissue is used. Assuming this is right, it seems reasonable to waive the requirement for informed consent for epidemiological research.

To take a second example, on the contribution model, individuals are involved in research that gathers data from their medical records. As a result, individuals have an interest in having a say in whether they contribute to such research. With that said, such research seems to represent less of a contribution on the part of sources in the sense that sources contribute information only, they don't contribute part of themselves.[27] This suggests individuals have a much less weighty interest in determining whether their medical records are used for research purposes, hence, investigators have little reason to obtain their informed consent in these cases. Therefore, it appears, on the contribution model, that consent can be waived for research on medical records provided there is no reason to think the research may be of special concern to sources. Of course, although individuals' status as contributors does not imply a need to obtain their consent in this case, their status as individuals with an interest in avoiding harms may. That is, consent should be obtained for research that poses serious risks even when individuals' contribution to the research is minimal.

[27] This example suggests that any complete account of the contribution model will have to admit of varying degrees of contribution.

IMPLICATIONS FOR OTHER ISSUES IN BIOETHICS

The contribution model recognizes that individuals may be involved in research, in the sense of contributing to the research in question, even when it does not pose any risks to them and does not ask them to do anything. To the extent this model applies to research participation in general, it may help illuminate other debates in the ethics of human subjects research. To take just one example, Robert Truog has argued that the requirement for informed consent should be waived for a trial of two antibiotics that have similar side effect profiles when it is unknown which medication is better.[28] Truog points out that, given the similar risk/potential benefit profiles, patients are unlikely to prefer one medication over the other. He concludes that the process of obtaining consent is unlikely to serve the patients in any meaningful way.

Truog bases his argument on the claim that the obligation to seek consent depends upon 'the risk-benefit ratios of the intervention and the alternatives, as well as the degree to which the patient would be expected to have preferences about the various options for diagnosis or treatment that are under investigation.'[29] Recognition of the contribution model makes clear that these are not the only factors relevant to whether consent should be obtained: the fact that individuals are being asked to contribute to the research project provides a prima facie claim that their consent should be obtained.

Whether this prima facie claim is overridden in the kinds of cases that Truog imagines depends upon the weight of individuals' claim to have a say and the nature of the say they should have. The present point is not to determine whether, in these cases, individuals' interests are sufficiently weighty to require their consent. Instead, the point is that the purpose of obtaining individuals' informed consent for research participation goes beyond giving them a choice between their various research options, and includes giving them a say in whether they contribute to the research project in question.[30] Hence, the fact that individuals are very likely indifferent

[28] R. Truog. Is informed consent always necessary for randomized, controlled trials. *New England J Med* 1999; 340: 804–806.

[29] *Ibid.*

[30] In addition, any psychological benefits of contributing to research require that individuals *know* they are making a contribution. This would be another reason to obtain their consent.

between their research options does not necessarily imply that there is no reason to obtain their informed consent.

CONCLUSION

The debate over when investigators should obtain consent for research on anonymizable biological samples suggests a new paradigm for understanding individuals' involvement in research. On the subject model, there is no reason to solicit sources' informed consent because research using anonymized samples poses no direct risks to sources. Similarly, on the experiential model, there is no reason to solicit sources' informed consent because, and this is particularly clear for samples that were obtained in the past, anonymized research may not affect sources personally. The fact that some writers argue for informed consent, nonetheless, points to a third model of sources' involvement in research.

The contribution model recognizes that individuals' interests extend beyond their own experiences. In particular, individuals have interests in the projects to which they contribute. By taking these interests into account, it becomes clear that many of the arguments for and against obtaining sources' informed consent have been overstated. Those who argue that investigators have no reason to obtain informed consent for anonymizable research implicitly assume an overly narrow understanding of sources' relevant interests, one that ignores their potential interests in determining whether they contribute to the research in question. Others recognize that investigators have a reason to obtain sources' informed consent for anonymizable research, but often conclude that consent should be obtained whenever possible. This view implicitly assumes that individuals' interests in having a say always outweighs any reasons not to obtain consent. There are two problems with this view.

First, individuals can have competing interests in not having a say. In addition, individuals often have less weighty interests in controlling precisely which research projects they contribute to. Thus, serious burdens in obtaining their consent can outweigh their interest in determining whether they contribute to a specific research project. Finally, individuals' autonomy interests do not imply that they should control every aspect of their lives, including determining every project to which they contribute. Individuals can cede control over particular projects. In the case of research with biological samples, individuals can ethically give consent for future research purposes in general without having

to know about and approve every individual use of their samples.

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